REMARKS

Claims 1-8 remain in the application. Claims 1-3 and 6-8 are in independent form.

Applicants express their gratitude for courtesies extended by the Examiner during a telephonic interview conducted Wednesday, May 12, 2004. During the telephonic interview, the presently pending claims were discussed along with proposed amendments.

In order to further prosecution, the claims have been amended to more specifically recite the nitric oxide donors that can be used to promote new neuron growth. Support for the nitric oxide donors can be found in the specification as originally filed at page 5, lines 1-10, wherein there are specifically disclosed examples of nitric oxide donors that are capable of promoting new neuron growth.

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Moskowitz patent. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by the Moskowitz patent, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

The Office Action states that the Moskowitz patent teaches a method of treating strokes and the resulting neurological damage by administering nitric oxide releasing compounds. The therapeutic target of the Moskowitz approach is the reduction of cerebral infarction (i.e. volume of dead brain tissue) after ischemic stroke, which is stroke caused by a lack of blood flow to the brain. Moskowitz seeks to increase blood flow to the brain to limit volume of infarction. In other words, the patent discloses treating injured brain in an attempt to salvage brain tissue. The treatment disclosed in the Moskowitz patent is limited to times early after onset of ischemic stroke when blood flow increase can increase the volume of blood flowing to the damaged tissue. In the

Moskowitz patent, there is disclosed that the reduction of the infarction is mediated by administration of a substrate for NO before or early (within the first 1-2 hours) after stroke. The substrate is given from 16 hours before stroke to 2 hours after stroke. This enhances blood flow to the brain and thereby counteracts some of the loss of blood flow initiated by the stroke. The Moskowitz patent states in column 1 line 31 that, "the nervous system lacks the ability to regenerate," in column 1 lines 40- 44, "the ultimate size of the infarct which forms the basis of medical therapy is the extent of vascular support." Thus, according to the Moskowitz patent, the intervention must be designed to improve blood flow and thereby to reduce the ischemic lesion, because when the lesion is complete, the lesion cannot be reduced by treatment.

The Moskowitz patent also discloses that the brain/neurons cannot regenerate. The data presented in the Moskowitz patent only relate to treatment of a model of ischemic stroke with a substrate of NO. All data presented by Moskowitz show a reduction of volume of cerebral infarction, dilation of blood vessels, and, as noted in column 3 line 18, the approach of the Moskowitz patent is to "limit the extent of stroke-associated infarct." The patent discloses that treatment should preferably begin shortly after the initiation of stroke and preferably at any point in time prior to the completion of the infarction process. There is disclosed that, "treatment may be initiated, however, at any point in time prior to the completion of the infarction process." The disclosure also provides that "in certain instances, the methods of the invention may be used to treat a patient after the completion of a stroke episode." There is no disclosure of what those "instances" are or how they relate to treatment and thus, the disclosure does not enable one of skill in the art to ascertain the possibility that any beneficial effects are afforded a patient who has the NO compound administered post-stroke. Further, there is no disclosure that treatment at any point subsequent to the completion of the stroke would function in the desired manner. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile. Further, the Moskowitz patent and all other prior art disclosures disclose methods for limiting the infarction process or increasing the blood flow to the areas of the brain that

were damaged by stroke. There is no disclosure for the regeneration of neurons as is disclosed in the presently pending independent claims.

In contradistinction, the presently pending independent claims claim NO donors, PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on the volume of infarction. As disclosed throughout the currently pending patent application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the treatment. Further, the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy can be administered days and weeks after the injury, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, and can even be administered 24 or more hours after stroke. The method and compound of the presently pending independent claims claim inducing brain remodeling an event that is independent of the reduction of the volume of cerebral infarction. There is no connection or association of reduction of volume of cerebral infarction and with the production of new brain cells. There is no requirement of the presence of a NO donor to induce brain remodeling and functional benefit.

The Office Action has maintained that Applicants' definition of promoting neurogenesis includes proliferation of parenchymal cells and as such, is much broader than originally suggested. However, when read more specifically, the definition of promoting neurogenesis is defined as "new neuronal growth or enhanced growth of existing neurons, as well as growth and proliferation of parenchymal cells and cells that promote tissue plasticity." The recovery includes the increase of parenchymal cells as a result of the proliferation of new neurons, therefore, the parachymal cells are increased as a result of the neurogenesis and thus, are an effect of neurogenesis. Additionally, the methodology disclosed in the Moskowitz patent does not initiate neurogenesis. In fact, the Moskowitz patent discloses that neurons cannot regenerate. It is actually contrary to the common knowledge of those in skill in the art to have

administered any compounds after the completion of the stroke. Instead, it was believed by those of skill in the art that upon completion of the stroke, an individual was no longer able to be treated and must instead learn to survive with the results of the stroke.

Further, as detailed in the attached Declaration by the inventor, new data has been recently generated. This data was obtained by following the methodology disclosed in the Moskowitz patent. The results indicate that the method of the Moskowitz patent does reduce ischemic damage, however, there is no neurogenesis, new neuron growth, that occurs. As stated above, the method of the Moskowitz patent does not create the results that are disclosed in the presently claimed invention.

Since the Moskowitz patent does not disclose or suggest the method and compound of the presently pending independent claims, the claims are patentable over the Moskowitz patent, and reconsideration of the rejection is respectfully requested.

Claim 6 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Bredt et al. reference. Reconsideration of the rejection under 35 U.S.C. §103(a) over the Bredt et al. reference, as applied to the claims is also respectfully requested.

It is Hornbook Law that before two or more references may be combined to negative patentability of a claimed invention, at least one of the references must teach or suggest the benefits to be obtained by the combination. This statement of law was first set forth in the landmark case of Ex parte McCullom, 204 O.G. 1346; 1914 C.D. 70. This decision was rendered by Assistant Commissioner Newton upon appeal from the Examiner-in-Chief and dealt with the matter of combination of references. Since then many courts have over the years affirmed this doctrine.

The applicable law was more recently restated by the Court of Appeals for the Federal Circuit in the case of ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572,1577, 221 U.S.P.Q. 929 (Fed. Cir. 1984). In this case the Court stated, on page 933, as follows:

> Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under Section 103 teachings of references can be combined only if there is some suggestion or incentive to do so. The prior art of record fails to provide any

> such suggestion or incentive. Accordingly we hold that the court below erred as a matter of law in concluding that the claimed invention would have been obvious to one of ordinary skill in the art under section 103.

This Doctrine was even more recently reaffirmed by the CAFC in Ashland Oil, Inc. v. Delta Resins and Refractories, Inc., et al., 776 F.2d 281,297, 227 U.S.P.Q. 657,667. As stated, the District Court concluded:

> Obviousness, however, cannot be established by combining the teachings of the prior art to produce the claimed invention unless there was some teaching, suggestion, or incentive in this prior art which would have made such a combination appropriate.

The Court cited ACS Hospital Systems, Inc. in support of its ruling. This Doctrine was reaffirmed in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995).

The Office Action states that the Bredt et al. reference teaches that nitric oxide is a diffusible multifunctional second messenger that has been implicated in numerous physiological functions in mammals ranging from dilation of blood vessels to immune response and potentiation of synaptic transmission. However, when read more specifically, there is no disclosure in the Bredt et al. reference for the potentiation of synaptic transmission. What is disclosed is that nitric oxide influences neurotransmitter release. Data is described on page 185 showing that NOS inhibitors block the release of neurotransmitters. There is no disclosure that the potentiation of synaptic transmission is related to synaptogenesis. The effect of NO on the release of neurotransmitters is not associated in any way with synaptogenesis. Synaptogenesis is the formation of new synapses, new connections in the growth and extension of synaptic and dendritic structures. The structural change of neurons is unrelated to the potentiation of neurons to release chemicals associated in electrical communications (i.e., neurotransmitters). Thus, NO as a neurotransmitter or a modulator of neurotransmission is distinct from NO as a promoter of synaptogenesis and one function is not related to the other. Further, the fact that NO has been implicated in numerous physiological and pathophysiological functions (i.e., cell death as extensively discussed on page 187-191 of the Bredt et al. reference) does not imply that NO is involved in brain plasticity and the production of new neurons, blood vessels, or synapses. There is no suggestion or teaching in the Bredt et

al. reference of the ability of NO to induce functional improvement in brain plasticity after stoke or neural injury. Thus, the Bredt et al. reference does not disclose or suggest the invention as claimed in the presently pending independent claims, and as such the presently pending independent claims are patentable over the Bredt et al. reference and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

It is respectfully requested that the present amendment be entered in order to place the application in condition for allowance or at least in better condition for appeal. The application is placed in condition for allowance as it addresses and resolves each and every issue that remains pending. Claims have also been amended to clearly distinguish over the prior art. The application is made at least in better condition for appeal as the amendment removes many issues thereby simplifying the issues on appeal. Further, the claims have been amended to more specifically define the invention while raising no new issues that would require any further searching. Rather, the amendments have been made in view of comments made in the Office Action that clearly distinguish the presently pending claims over the cited prior art. Hence, it is respectfully requested that the amendment be entered.

This amendment could not have been made earlier as the amendment further defines the claims over the prior art in accordance with the suggestion made in the Office Action, the suggestion first being made in the outstanding Office Action. Hence, since there remain no further issues to be resolved, it is respectfully requested that the present amendment be entered.

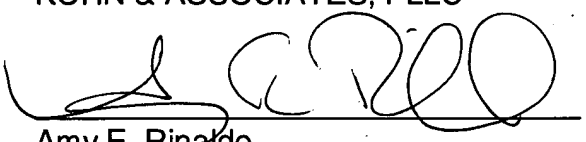
In conclusion, it is respectfully requested that the present amendment be entered in order to place the application in condition for allowance, which allowance is respectfully requested.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES, PLLC



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Dated: May 19, 2004

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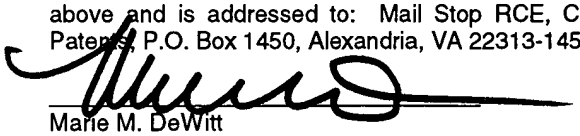

Marie M. DeWitt

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: CHOPP ET AL.

Serial No.: 10/018,201 Group Art Unit: 1614

Filed: 04/02/02 Examiner: JAGOE, Donna A

For: NITRIC OXIDE DONORS FOR INDUCING NEUROGENESIS

Attorney Docket No: 1059.00063

Commissioner for Patents
Mail Stop RCE
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF MICHAEL CHOPP

I, Michael Chopp, do hereby say that:

1. I am a co-inventor of the invention set forth and claimed in the above-captioned patent application.

2. I am an expert in the field of neurogenesis.

3. I have reviewed in detail the Office Action issued November 19, 2003, the Amendment Under Rule 1.116 filed in response thereto, and the Advisory Action dated May 3, 2004. Specifically, I have reviewed the rejection of claims 1-8 as being unpatentable over the Moskowitz patent.

4. The Office Action states that the Moskowitz patent teaches a method of treating strokes and the resulting neurological damage by administering nitric oxide releasing compounds. The therapeutic target of the Moskowitz approach is the reduction of cerebral infarction (i.e. volume of dead brain tissue) after ischemic stroke that is stroke caused by a lack of blood flow to the brain. Moskowitz seeks to increase blood flow to the brain to limit volume of infarction. In other words, the patent discloses treating injured brain in an attempt to salvage brain tissue. The treatment disclosed in the Moskowitz patent is limited to times early after onset of ischemic stroke when blood flow increase can increase the volume of blood flowing to the damaged tissue. In the Moskowitz patent, there is disclosed that the reduction of the infarction is mediated by

administration of a substrate for NO before or early (within the first 1-2 hours) after stroke. The substrate is given from 16 hours before stroke to 2 hours after stroke. This enhances blood flow to the brain and thereby counteracts some of the loss of blood flow initiated by the stroke. The Moskowitz patent states in column 1 line 31 that, "the nervous system lacks the ability to regenerate," in column 1 lines 40- 44, "the ultimate size of the infarct which forms the basis of medical therapy is the extent of vascular support." Thus, according to the Moskowitz patent, the intervention must be designed to improve blood flow and thereby to reduce the ischemic lesion, because when the lesion is complete, the lesion cannot be reduced by treatment there is no benefit.

5. The Moskowitz patent also discloses that the brain cannot regenerate. The data presented in the Moskowitz patent only relate to treatment of a model of ischemic stroke with a substrate of NO. All data presented by Moskowitz show a reduction of volume of cerebral infarction, dilation of blood vessels, and, as noted in column 3 line 18, the approach of the Moskowitz patent is to "limit the extent of stroke-associated infarct." The patent discloses that treatment should preferably begin shortly after the initiation of stroke and preferably at any point in time prior to the completion of the infarction process. There is disclosed that, "treatment may be initiated, however, at any point in time prior to the completion of the infarction process." The disclosure also provides that "in certain instances, the methods of the invention may be used to treat a patient after the completion of a stroke episode." There is no disclosure of what those "instances" are or how they relate to treatment and thus, the disclosure does not enable one of skill in the art to ascertain the possibility that any beneficial effects are afforded a patient who has the NO compound administered post-stroke. Further, there is no disclosure that treatment at any point subsequent to the completion of the stroke would function in the desired manner. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile. Further, the Moskowitz patent and all other prior art disclosures disclose methods for limiting the infarction process or increasing the blood flow to the areas of the brain that were damaged by stroke. There is no disclosure for the regeneration of neurons as is disclosed in the presently pending independent claims.

6. In contradistinction, the presently pending independent claims claim NO donors, PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on

the volume of infarction. As disclosed throughout the currently pending patent application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the treatment. Further, the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy can be administered days and weeks after the injury, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, and can even be administered 24 or more hours after stroke. The method and compound of the presently pending independent claims claim inducing brain remodeling an event that is independent of the reduction of the volume of cerebral infarction. There is no connection or association of reduction of volume of cerebral infarction and with the production of new brain cells. There is no requirement of the presence of a NO donor to induce brain remodeling and functional benefit.

7. Further, new data has been recently generated. This data was obtained by following the methodology disclosed in the Moskowitz patent. The results indicate that the method of the Moskowitz patent does reduce ischemic damage, however, there is no neurogenesis, new neuron growth, that occurs. As stated above, the method of the Moskowitz patent does not create the results that are obtained by the presently claimed invention as set forth in the pending amended independent claims.

8. The data is attached hereto as Appendix A..

9. In view of the above, it is my opinion, based on our research results, that one skilled in the art could not utilize the teachings of the cited prior art to derive the present invention. Rather, we utilized a significantly different approach, not at all utilizing the methods or data set forth in the cited prior art to derive the invention. Thus, we unexpectedly derived the claimed subject matter of the present invention.

The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true.

DATE: May 19, 2004

_____
Michael Chopp

APPENDIX A

L-Arginine in acute stroke treatment

Animal model and Experimental protocol

All experimental procedures have been approved by the Care of Experimental Animals Committee of Henry Ford Hospital. Male Wistar rats weighing 280-310g were anesthetized with halothane (1-3.5% in a mixture of 70% N_2O and 30% O_2) using a face mask. The right femoral vein was cannulated with a PE-50 catheter for drug administration. A length of 18.5 to 19.0 mm 4-0 surgical nylon filament, with its tip rounded by heating near flame, was advanced from the external carotid artery (ECA) into the lumen of the internal carotid artery (ICA) until it blocked the origin of the middle cerebral artery (MCA)[1].

Ischemic rats were randomly divided into two groups in which rats received L-Arginine (300mg/kg, i.v, bolus, Group 1, n=6) or D-Arginine (300mg/kg, i.v, bolus, Group 2, n=6) at 5 minutes and 1 hour after onset of ischemia. All rats were sacrificed at 7 days after treatment.

BrdU labeling:

To label proliferating cells in the subventricular zone, animals received daily intraperitoneal (i.p) injections of bromodeoxyuridine (BrdU, 50mg/kg, Sigma) for 7 consecutive days starting at the first experimental day.

Histology:

Measurement of infarct volume:

A total 4 coronal blocks (2 mm thickness) of brain tissue between AP + 10.6 mm - +2.28 mm for each rat were embedded in paraffin and coronal sections from each block were cut in 6μm thick and stained with hematoxylin and eosin (H&E). Each H&E stained coronal section was evaluated at 2.5 X magnification) using a Global Lab Image analysis program (Data Translation, Marlboro, MA). The areas of infarction and the ipsilateral hemisphere (mm^2) were calculated on H&E stained sections by tracing the areas on the computer screen, and the volumes (mm^3) were determined by integrating the appropriate area with the section interval thickness. To reduce errors associated with processing of tissue for histological analysis, the infarct volume was presented as the percentage of infarct volume to the contralateral hemisphere[1].

Immunohistochemistry: For BrdU immunostaining, DNA was first denatured by incubating brain sections (6 μm) in 50% formamide 2X SSC at 65^{0}C for 2 h and then in 2N HCl at 37°C for 30 min[3,4]. Sections were then rinsed with Tris buffer and treated with 1% of H_2O_2 to block endogenous peroxidase. Sections were incubated with a primary antibody to BrdU (1:100) at room temperature for 1 h and then incubated with biotinylated secondary antibody (1:200, Vector, Burlingame, CA) for 1 h. Reaction product was detected using 3'3'-diaminobenzidine-tetrahydrochloride (DAB, Sigma).

Quantification: Numbers of BrdU immunoreactive cells were counted using stereological principles [3,4]. BrdU immunostained sections were digitized using a 40x objective (Olympus BX40) via the MCID computer imaging analysis system (Imaging Research, St. Catharines, Canada) and numbers of BrdU immunoreactive nuclei were counted on a computer monitor to improve visualization and in one focal plane to avoid over-sampling. Structures were sampled either by selecting predetermined areas on each section (OB) or by analyzing entire structures on each section (SVZ and dentate gyrus). All BrdU immunoreactive-positive nuclei in these areas

are presented as the number of the BrdU immunoreactive cells /mm^2 and data shown are mean ± SE. Density for the selected several sections was averaged to obtain a mean density value for each animal.

Subventricular zone: Every 40th coronal section was selected from each rat for a total of 7 sections between AP + 10.6 mm - genu corpus callosum- and AP+ 8.74 mm-anterior commissure crossing [2]. BrdU immunoreactive-positive nuclei were counted in the subventricular zone.

OB: Every 20th section was selected from each rat for a total of 6 sections from the sagittal series of the OB/frontal cortex. Four areas (300 X 300 μm) in the granule cell layer (GCL) of the OB were analyzed on each section.

Dentate gyrus: Every 50th coronal section was selected from each rat for a total of 8 sections between AP +5.86 mm and AP +2.96 mm including the hilus, subgranular zone (SGZ), inner first to second and third of the granule cell layer (GCL). The SGZ, defined as a two-cell body wide zone along the border of the GCL and the hilus, was combined with the GCL for quantification.

Results:

Treatment of acute stroke with L-Arginine significantly ($p<0.05$) reduced infarct volume compared with treatment with D-Arginine that does not increase NO (Fig. 1A), which is consistent with previous reports (Morikawa). However, rats treated with D-Arginine exhibited significant increases in numbers of BrdU immunoreactive cells in the olfactory bulb compared with rats treated with L-Arginine (Fig. 2). Furthermore, there is a significant correlation between numbers of BrdU immunoreactive cells and infarct areas (Fig. 1B). These data indicate that treatment of acute stroke with L-Arginine reduces infarct volume but does not enhance neurogenesis and that increases in neurogenesis appear to be related to size of infarct volume.

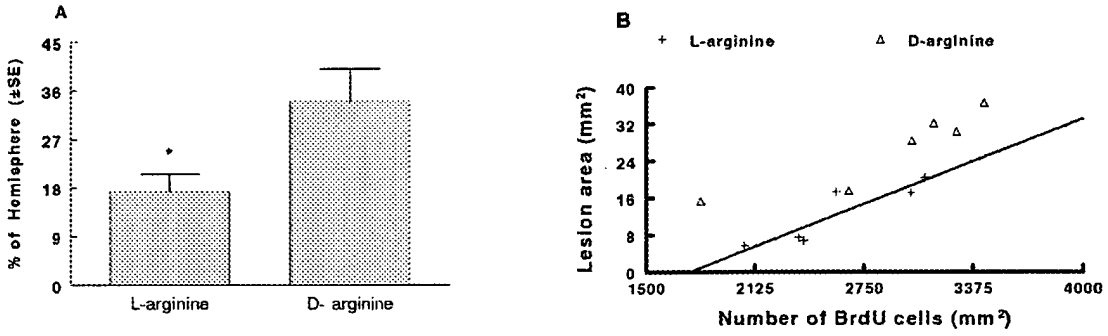

Fig.1 Infarct volume (A) and correlation between infarct area and numbers of BrdU immunoreactive cells (B). There was a significant correlation between numbers of BrdU positive cells and lesion area ($p=0.0001$) with 0.9 correlation coefficient. *$p<0.05$ vs D-Arginine group and n=6/group.

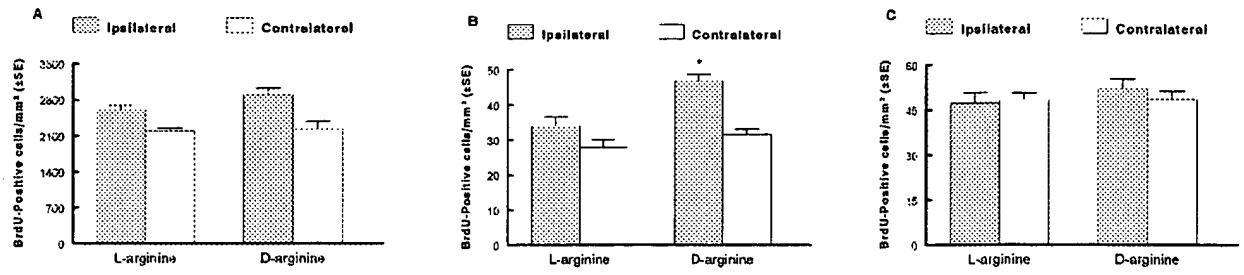

Fig. 2 Numbers of BrdU positive cells in the subventricular zone (A), olfactory bulb (B), and dentate gyrus (C). *p<0.05 vs L-Arginine group and n=6/group.

References:

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3. Liu J, Solway K, Messing RO, et al. Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. J Neurosci 1998; **18:**7768-7778.

4. Zhang RL, Zhang ZG, Zhang L, Chopp M (2001) Proliferation and differentiation of progenitor cells in the cortex and the subventricular zone in the adult rat after focal cerebral ischemia. Neuroscience 2001;**105**:33-41.

5. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation . J Neurosci 1996; **16:** 2027- 2033.